Production of Inhaler Grade Lactose by Crystallization

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Konrad Raimund Shaffer

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Abstract

This work focused on producing Inhaler grade lactose (IGL) directly by crystallization. IGL is a high purity lactose excipient meeting a range of precise particle size distribution specifications. The 50 percent particle size (d_{50}) on a volume basis desired for this work was in the range of 50 to 90 μm, and a span less than 1. IGL is commonly used as a drug carrier in dry particle inhalers. Typical industrial lactose crystallization produces lactose with a d_{50} greater than 200 μm and a span of around 2. The large span has been attributed to successive nucleation events during the growth phase and growth rate dispersion. Costly additional processing is currently required to produce IGL, generally in the form of sieving and milling.

Initially the crystallization literature was reviewed with a specific focus on alternative methods for producing a narrow particle size distribution. From this, three methods were mathematically modelled for their ability to produce IGL. Crystallization in droplets literature and model predictions showed great potential for targeting a particle size distribution with a very low span directly from crystallization; however issues arose with scalability and potential contamination if not using a lactose or water carrier phase. Subsequent crystallization product stream processing via a hydrocyclone or inclined settler also showed the ability, in theory, to produce IGL; however both these methods were deemed as additional processing and a novel crystallization process was desired. This led to the development of the continuous settling crystallizer (CSC).

The CSC consists of a vertical column, where a pre-nucleated feed stream enters near the bottom of the column and flows out the top, all under laminar conditions. Inside the column only growth occurs as additional nucleation is limited by the chosen column conditions. The CSC incorporates the key elements revealed from the literature for achieving a narrow span of a single nucleation event and a method to counteract growth rate dispersion. Slow growing crystals travel further up the column than fast growing crystals before growing to the terminal particle settling diameter, opposing flow, and settling out from the column and into the product stream. For a particular fluid velocity, the crystals settle out into the product stream at the same final particle size. Under laminar flow conditions a parabolic profile occurs across the column radius and the CSC theoretical model developed predicted a product d_{50} of 73 μm and a span of 0.47 for the chosen column conditions.

Lab scale experiments were then carried out for the CSC. The resulting product d_{50} was in the desired range of 50 to 90 μm, but the span ranged from 1.4 to 1.5. Column channelling, an area of high flow and subsequent low flow elsewhere, was suspected as the cause of the experimental deviations. The theoretical model was modified to include channelling and predictions matched the experimental product results well. Due to the high level of control required for the CSC it is recommended that a batch process is designed to efficiently produce IGL; this would incorporate a single nucleation event and a hydrocyclone cut.

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